

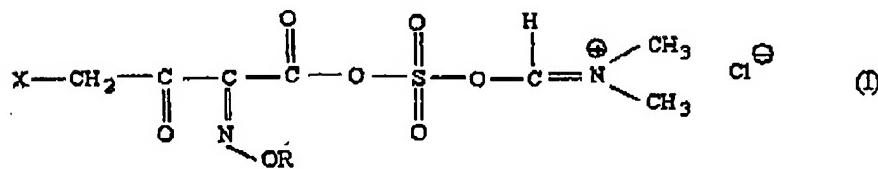
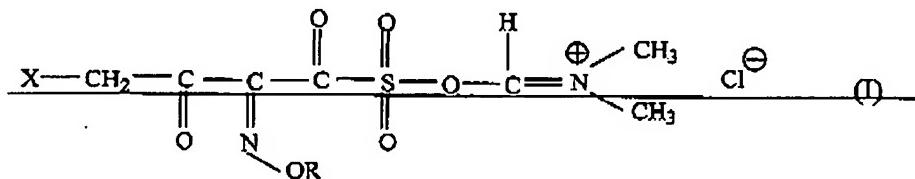
Application Number 10/540770  
 Response to the Office Action dated 03/20/2008

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) A novel 4-halo-2-oxyimino-3-oxo butyric acid-N, N-dimethyl formiminium chloride chlorosulfate of formula (I) useful in the preparation of cephalosporin antibiotics



wherein X is chlorine or bromine;

R is hydrogen, C<sub>1-4</sub> alkyl group, ~~an easily removable~~ a hydroxyl protective group; selected from trialkyl silyl ethers; trialkyl aryl silyl ethers; trialkyl stannylyl ethers; trityl; tetrahydropyranyl; alkyl or aryl sulphonates selected from tosyl, mesyl, and besyl; boron or aluminum containing two alkyl groups; unsubstituted benzyl; or

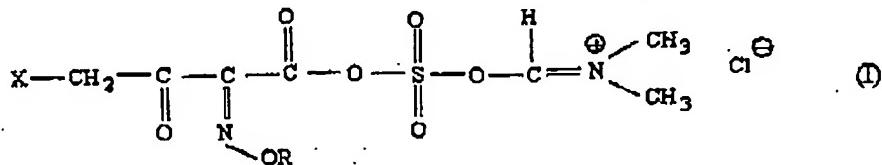
-CH<sub>2</sub>COOR<sub>5</sub>, or -C(CH<sub>3</sub>)<sub>2</sub>COOR<sub>5</sub>;

wherein R<sub>5</sub> is hydrogen; or ~~an easily a~~ hydrolysable ester group selected from lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxy methyl,

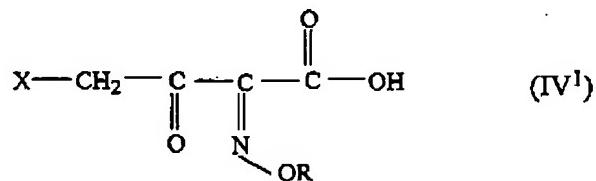
Application Number 10/540770  
Response to the Office Action dated 03/20/2008

1-acetoxy ethyl, and 1-pivaloxyethyl; lower alkoxycarbonyloxyalkyl esters; alkoxymethyl esters; lower alkyl amino methyl; benzyl ester; and cyanomethyl ester.

2. (Currently Amended) A process for preparation of compound of formula (I)



comprising reacting 4-halo-2-oxyimino-3-oxobutyric acid of formula (IV<sup>1</sup>),



wherein X is chlorine or bromine;

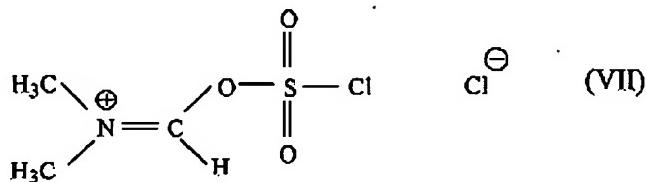
R is hydrogen, C<sub>1-4</sub> alkyl group, ~~an easily removable a hydroxyl protective group, selected from trialkyl silyl ethers; trialkyl aryl silyl ethers; trialkyl stannyly ethers; trityl; tetrahydropyranyl; alkyl or aryl sulphonates selected from tosyl, mesyl, and besyl; boron or aluminum containing two alkyl groups; unsubstituted benzyl; or~~

-CH<sub>2</sub>COOR<sub>5</sub>, or -C(CH<sub>3</sub>)<sub>2</sub>COOR<sub>5</sub>

wherein R<sub>5</sub> is hydrogen; or ~~an easily a hydrolysable ester group selected from lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxy methyl, 1-acetoxy ethyl, and 1-pivaloxyethyl; lower alkoxycarbonyloxyalkyl esters; alkoxymethyl esters; lower alkyl amino methyl; benzyl ester; and cyanomethyl ester[.]~~

Application Number 10/540770  
Response to the Office Action dated 03/20/2008

with N,N-dimethylformiminium chloride chlorosulphate of formula (VII)

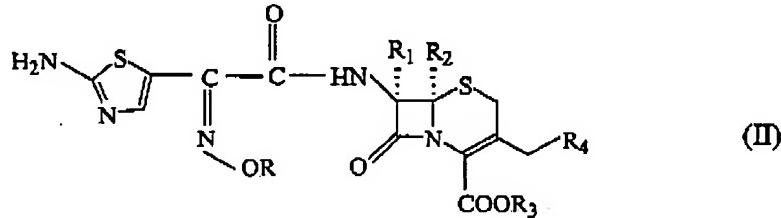


in an organic solvent at a temperature ranging from  $-30^{\circ}\text{C}$  to  $-15^{\circ}\text{C}$ .

3. (Currently Amended) A process according to Claim 2, wherein the organic solvent is selected from chlorinated solvents such as selected from dichloromethane, dichloroethane, or and chloroform; aromatic hydrocarbons such as selected from benzene or and toluene; and nitriles such as selected from acetonitrile, propionitrile or and butyronitrile.

4. (Currently Amended) A process according to Claim 2, wherein the molar ratio of compound of formula (VII) to compound of formula (IV<sup>1</sup>) is between 1.1 to 1.3.

5. (Currently Amended) A process for preparation of a cephalosporin compound of formula (II),



wherein

R is hydrogen, C<sub>1-4</sub> alkyl group, an easily removable a hydroxyl protective group, selected from trialkyl silyl ethers; trialkyl aryl silyl ethers; trialkyl stannyl ethers; trityl;

Application Number 10/540770  
Response to the Office Action dated 03/20/2008

tetrahydropyranyl; alkyl or aryl sulphonates selected from tosyl, mesyl, and besyl; boron or aluminum containing two alkyl groups; unsubstituted benzyl; or

$-\text{CH}_2\text{COOR}_5$ , or  $-\text{C}(\text{CH}_3)_2\text{COOR}_5$ ;

wherein  $R_5$  is hydrogen; or an easily hydrolysable ester group selected from lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxy methyl, 1-acetoxy ethyl, and 1-pivaloxyethyl; lower alkoxy carbonyloxyalkyl esters; alkoxy methyl esters; lower alkyl amino methyl; benzyl ester; and cyanomethyl ester[[-]].

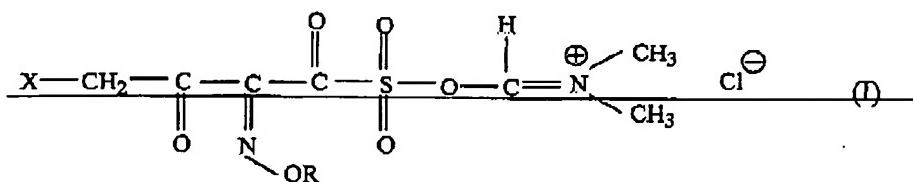
$R_1$  is hydrogen or  $[-]\text{OCH}_3$ ;

$R_2$  is hydrogen;

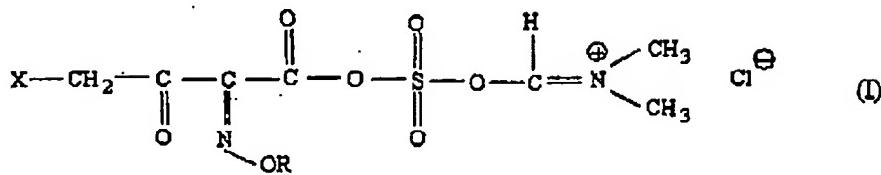
$R_3$  is hydrogen, a negative charge or together with the  $\text{COO}^-$  group to which  $R_2$  is attached is an ester, or an alkali or alkaline earth metal, ester selected from the group of lower alkyl esters; alkanoyloxy alkyl esters selected from acetoxy methyl, pivaloxymethyl, 1-acetoxyethyl, and 1-pivaloxyethyl ester; lower alkoxy carbonyloxyalkyl esters selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxyethyl ester; alkoxy methyl esters; lower alkyl aminomethyl esters; acetamidomethyl ester; benzyl ester; and cyanomethyl ester.

$R_4$  is hydrogen or is a substituent useful in cephalosporin chemistry selected from unsubstituted and substituted alkyl; and unsubstituted and substituted alkenyl; wherein substituted alkyl and/or alkenyl being substituted by alkoxy, heterocyclicthio, heterocycliccarbonylthio, alkylcarbonyloxy, or heterocyclyl;

comprising reaction of compound of formula (I)



Application Number 10/540770  
Response to the Office Action dated 03/20/2008

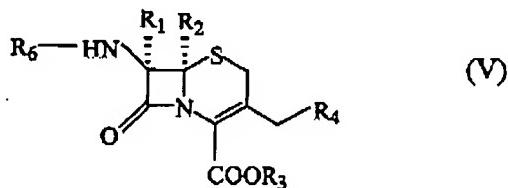


wherein X is chlorine or bromine; R and R<sub>5</sub> are selected from corresponding groups listed for those of formula (II) above

R is hydrogen, C<sub>1-4</sub> alkyl group, an easily removable hydroxyl protective group, -CH<sub>2</sub>COOR<sub>5</sub>, or C(CH<sub>3</sub>)<sub>2</sub>COOR<sub>5</sub>

wherein R<sub>5</sub> is hydrogen or an easily hydrolysable ester group

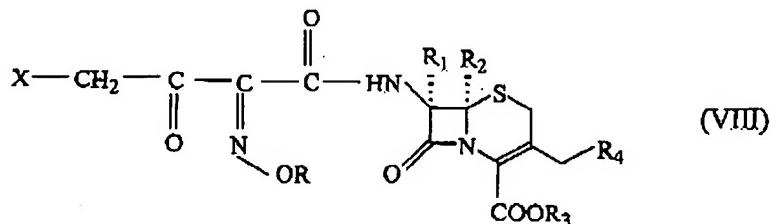
with 7-amino cephalosporanic acid of formula (V),



wherein R<sub>1</sub> is hydrogen or -OCH<sub>2</sub>; and R<sub>2</sub> are selected from corresponding groups listed for those of formula (II) above; R<sub>3</sub> is selected from a group listed for R<sub>3</sub> of formula (II) above or a trialkyl silyl group; hydrogen, a negative charge or together with the COO<sup>-</sup> group to which R<sub>3</sub> is attached is an ester, or an alkali or alkaline earth metal, or is a silyl group; R<sub>4</sub> is selected from a group listed for R<sub>4</sub> of formula (II) above; hydrogen or is a substituent useful in cephalosporin chemistry; R<sub>6</sub> is hydrogen or a trialkyl silyl group with the proviso that, when R<sub>3</sub> is hydrogen, R<sub>6</sub> is also hydrogen; when R<sub>3</sub> is a trialkyl silyl group, R<sub>6</sub> is also a trialkyl silyl group; and when R<sub>3</sub> is an ester, or an alkali or alkaline earth metal R<sub>6</sub> is hydrogen

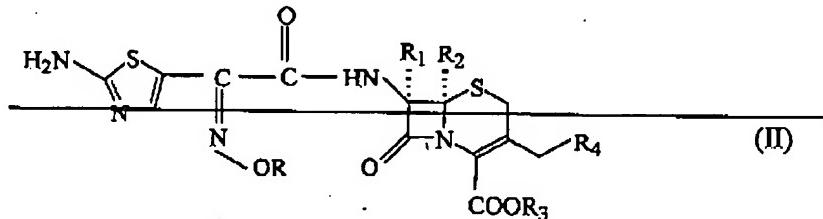
Application Number 10/540770  
Response to the Office Action dated 03/20/2008

to give 7-[(4-halo-2-oxyimino-3-oxobutyramido)-3-substituted-3-cephem-4-carboxylic acid of formula (VIII),



wherein X, R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> have are corresponding groups listed for those of formula (I) or (II) above the same meanings as defined herein earlier, and R<sub>3</sub> is hydrogen, a negative charge or together with the COO<sup>-</sup> group to which R<sub>3</sub> is attached is an ester, or an alkali or alkaline earth metal.

followed by cyclisation of compound (VIII) with thiourea, to give compound of formula (II),



wherein R and R<sub>5</sub> are as defined above; R<sub>4</sub> is hydrogen or OCH<sub>3</sub>; R<sub>5</sub> is hydrogen; R<sub>3</sub> is hydrogen, a negative charge or together with the COO<sup>-</sup> group to which R<sub>3</sub> is attached is an ester or an alkali or alkaline earth metal; R<sub>4</sub> is hydrogen or is a substituent useful in cephalosporin chemistry.

6. (Currently amended) A The process according to Claim 5, wherein the reaction of compound (I) and compound (V) to give compound (VIII) is carried out in an organic

Application Number 10/540770  
Response to the Office Action dated 03/20/2008

solvent and in the presence of a base at a temperature ranging from -80<sup>0</sup> C to -15<sup>0</sup> C[[,]].

7. (Currently amended) ~~A~~The process according to Claim [[5]]6, wherein the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons such as benzene and toluene; nitrile solvents such as acetonitrile, propionitrile and butyronitrile; and ethers such as tetrahydrofuran and dioxane.

8. (Currently amended) ~~A~~The process according to Claim [[5]]6, wherein the base is selected from N, N dimethyl aniline, diethyl amine, and pyridine.

9. (Currently amended) ~~A~~The process according to Claim 5, wherein the molar ratio of compound (I) to the cephalosporin compound (V) is between 1.1 to 2.0, preferably between 1.2 to 1.5.

10. (Currently Amended) ~~A~~The process according to Claim 5, wherein the preferred temperature is between -55<sup>0</sup> C to -25<sup>0</sup> C.

11. (Currently Amended) ~~A~~The process according to Claim 5, wherein the reaction of compound (VIII) and thiourea to give the cephalosporin compounds of formula (II) is carried out in a mixture of organic solvent and water and in the presence of a base at low to ambient temperature.

12. (Currently Amended) ~~A~~The process according to Claim [[5]]11, wherein the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons such as benzene and toluene;

Application Number 10/540770  
Response to the Office Action dated 03/20/2008

nitrile solvents such as acetonitrile, propionitrile and butyronitrile; and ethers such as tetrahydrofuran and dioxane.

13. (Currently Amended) ~~A~~The process according to Claim [[5]]6, wherein the base is selected from alkali metal carbonates, such as sodium carbonate, potassium carbonate and lithium carbonate; alkali metal hydrogen carbonates, such as sodium hydrogen carbonate and potassium carbonate; and alkali metal acetates, such as sodium acetate and potassium acetate.

14. (Currently Amended) ~~A~~The process according to Claim 5, wherein the a temperature at which the reaction is carried out is between -5<sup>0</sup> C to and 40<sup>0</sup> C, preferably between 10<sup>0</sup> C to 30<sup>0</sup> C.

15. (Currently Amended) ~~A~~The process according to Claim 5, wherein the compound of formula (II) is any one of

- i) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefdinir,
- ii) 7-[(Z)-2-(2-amino-4-thiazolyl)-2-methoxyimino)acetyl]amino-3-[(1Z)-2-(4-methyl-5-thiazolyl)ethenyl]-3-cephem-4-carboxylic acid, i.e. cefditoren and the pivaloyloxymethyl ester i. e. cefditoren pivoxil,
- iii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methylpyrrolodino) methyl-3-cephem-4-carboxylate i.e. cefepime,

Application Number 10/540770  
Response to the Office Action dated 03/20/2008

- iv) 7-[(Z)-2-(2-aminothiazol-4-yl)methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid i.e. cefetamet, and the pivaloyloxymethyl ester i. e. cefetamet pivoxil,
- v) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefixime,
- vi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-methyl-1H-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefmenoxime,
- vii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[[5-carboxymethyl)-4-methyl-2-thiazolyl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefodizime,
- viii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]-3-cephem-4-carboxylic acid i. e. cefoselis,
- ix) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid i.e. cefotaxime,
- x) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[92,3-cyclopenteno-1-pyridinium)methyl]-3-cephem-4-carboxylic acid i.e. cefpirome,

Application Number 10/540770  
Response to the Office Action dated 03/20/2008

- xi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate- i.e. cefpodoxime and the 1-methylethoxycarbonyloxy ether i. e. cefpodoxime proxetil,
- xii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-5,6,7-tetrahydroquinolinium-4-carboxylic acid inner salt i. e. cefquinome,
- xiii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethyl)oximinoacetamido}-3-[pyridinium]methyl-3-cephem-4-carboxylacid inner salt i. e. ceftazidime,
- xiv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(5-methyl-1,2,3,4-tetrazoyl)-methyl-3- cephem-4-carboxylic acid i. e. cefteram and the and the pivaloyloxymethyl ester i. e. ceferain pivoxil,
- xv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2-furanylcarbonyl)thio]methyl]- 3- cephem-4-carboxylic acid i. e. ceftiofur,
- xvi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid i. e. ceftizoxime,
- xvii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid i. e. ceftriaxone, and
- xviii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-ylthio)methyl]- 3-cephem-4-carboxylic acid i. e. cefuzonam.

Application Number 10/540770  
Response to the Office Action dated 03/20/2008

16. (New) The compound of formula (I) according to Claim 1, wherein R<sub>5</sub> is lower alkyl ester selected from methyl, ethyl, and tertiary butyl; lower alkoxy carbonyloxyalkyl ester selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropoxycarbonyloxyethyl; methoxymethyl ester; or acetamidomethyl ester.

17. (New) The process according to Claim 2, wherein R<sub>5</sub> is lower alkyl ester selected from methyl, ethyl, and tertiary butyl; lower alkoxy carbonyloxyalkyl ester selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropoxycarbonyloxyethyl; methoxymethyl ester; and acetamidomethyl ester.

18. (New) The process according to Claim 5, wherein R<sub>5</sub> is lower alkyl ester selected from methyl, ethyl, and tertiary butyl; lower alkoxy carbonyloxyalkyl ester selected from methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl, and 1-isopropoxycarbonyloxyethyl; methoxymethyl ester; and acetamidomethyl ester.

19. (New) The process according to Claim 5, wherein R<sub>3</sub> is lower alkyl ester selected from methyl, ethyl and tertiary butyl; and methoxymethyl ester.

20. (New) The process according to Claim 6, wherein the organic solvent is chlorinated solvent selected from dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbon selected from benzene and toluene; nitrile solvent selected from acetonitrile, propionitrile, and butyronitrile; or ethers selected from tetrahydrofuran and dioxane.

21. (New) The process according to Claim 11, wherein the organic solvent is chlorinated solvent selected from dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbon selected from benzene and toluene; nitrile solvent selected from acetonitrile, propionitrile, and butyronitrile; or ethers selected from tetrahydrofuran and dioxane.